

# ReNeuron

Corporate Presentation  
November 2019

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# A Leader in Cell-Based Therapeutics



Leading clinical stage cell therapy company  
Sites in the UK and Boston, US



Proprietary allogeneic stem cell technology platforms



Two clinical stage therapeutic candidates targeting  
unmet medical needs



Significant clinical validation milestones over the next  
24 months

# Proprietary Platform Technology

## hRPC

- Human retinal progenitor stem cell line
- Cryopreserved formulation allows global ship-and-store
- Positive early Phase 2a data in retinitis pigmentosa
- Partnered with Fosun Pharma for China



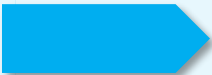
## CTX Cells

- Immortalised neural progenitor stem cell line
- 12 month shelf life (cryopreserved)
- Positive Phase 2a results in stroke disability
- Partnered with Fosun Pharma for China

## CTX-Derived Exosomes

- High-yielding human neural stem cell-derived nano-vesicles
- Proven ability to load with siRNA, miRNA and proteins
- Favourable distribution across the Blood Brain Barrier
- Potential as drug load/delivery vehicle and as a therapeutic

# Programme Pipeline

Programme	Indication	Pre-clinical	Phase 1	Phase 2	Next Milestone
<b>hRPC</b>	<b>Retinitis Pigmentosa</b>				Further Phase 2a data read-outs in H1 2020
<b>CTX cells</b>	<b>Stroke Disability</b>				PISCES III, pivotal, multi-centre U.S. Phase 2b study, data read-out expected H1 2021
<b>Exosomes</b>	<b>Drug Delivery</b>				Collaboration / Partnering deals targeted

# Human Retinal Progenitor Cells (hRPC)



# Human Retinal Progenitor Cells (hRPC)



hRPC: allogeneic cell-based therapeutic approach to retinal disease

- hRPCs differentiate into functional photoreceptors and integrate into retinal layers in pre-clinical models; integration may also enable durable trophic support
- Broad therapeutic potential across a range of retinal diseases
- Initially targeting inherited retinal degenerative diseases



Proprietary manufacturing process and controls allow for stable and high quantity GMP production

- Collaborations with Schepens Eye Research Institute and University College London
- Proprietary technology enabled development of GMP manufacturing process
- Cryopreserved formulation provides 9 month shelf life and enables local treatment worldwide

# Retinitis Pigmentosa: An Unmet Need

- RP is an inherited, degenerative eye disease<sup>1,2,3</sup>
  - Incidence of 1:4,000 in U.S. and worldwide
- >100 genes identified containing mutations leading to RP<sup>4</sup>
- Orphan Drug Designation in EU and U.S.
- FDA Fast Track Designation

**Therapeutic benefit of hRPC approach not dependent on genetic cause**



**NORMAL VIEW**



**VIEW WITH  
RETINITIS PIGMENTOSA**

<sup>1</sup> Hamel (2006) Orphanet J Rare Disease 1, 40;

<sup>2</sup> [https://nei.nih.gov/health/pigmentosa/pigmentosa\\_facts](https://nei.nih.gov/health/pigmentosa/pigmentosa_facts);

<sup>3</sup> NORD

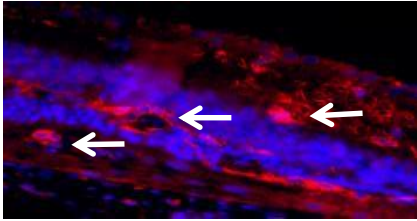
<sup>4</sup> <https://www.genome.gov/13514348/learning-about-retinitis-pigmentosa/>



# Pre-clinical Studies Support RPC Potential in Degenerative Retinal Disease

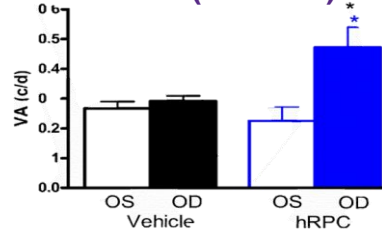
## hRPC in RCS Dystrophic Rats 12 Weeks Post-Injection

### hRPC Survival



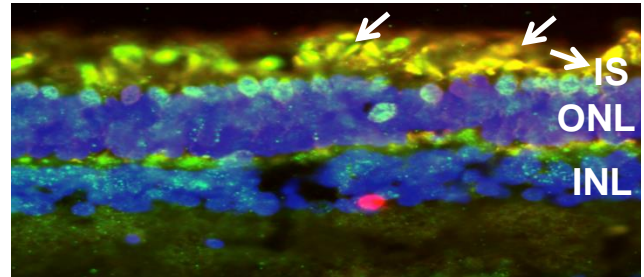
hRPC (red)/photoreceptors (blue); white arrows indicate hRPC cells within retinal layers

### Vision (via OKR)



OKR = optokinetic response; OS = oculus sinister (left eye); OD = oculus dextrus (right eye)

## pRPC in Pigs 4 Weeks Post-Injection



Transplanted donor cells (green); transplanted donor cells becoming photoreceptor cells (yellow) in the host retina (blue)  
IS = inner segments; ONL = outer nuclear layer; INL = inner nuclear layer

- Evidence that hRPC:
  - Integrated into host retina
  - Provided trophic support of host cells
  - Preserved vision based on OKR

- Evidence that pRPC:
  - Differentiated into retinal cells
  - Integrated into host retina
  - Required no immunosuppression

# Pre-Clinical Data Support a Durable Response

Species	Time after Treatment	Incidence of Survival
<b>Dystrophic RCS &amp; Normal Rats</b>	<b>28 weeks</b>	77%; 23/30 dystrophic RCS rats 70%; 7/10 normal control rats
<b>NIH-III Nude Mice</b>	<b>39 weeks</b>	33%; 15/45
<b>Mini Pigs</b> (allogeneic study mimicking the clinical scenario)	<b>12 weeks</b>	81%; 21/26  At 12 weeks a number of surviving pRPCs appeared to have migrated into the photoreceptor layer up to a depth of 2-3 layers, indicating cell integration.

**RPC cells survive for long periods in all species and survival is unaffected by the presence of disease**

# Clinical Development – Phase 1/2a

## Phase 1

- FIH, single ascending dose in subjects with established RP
  - Subjects with very poor visual potential
  - Four cohorts, three subjects each
  - Dose escalated to 1m cells
  - Formulation changed from fresh to cryopreserved cells
- Established safety in 1m cell dose in cryopreserved formulation

## Phase 2a

- 6-12 additional subjects with established RP
  - Patients with better visual potential
  - 10 subjects treated to date
- Primary endpoint: safety
- Secondary measures: visual acuity, visual field, retinal sensitivity and retinal structure

## U.S. Clinical Sites

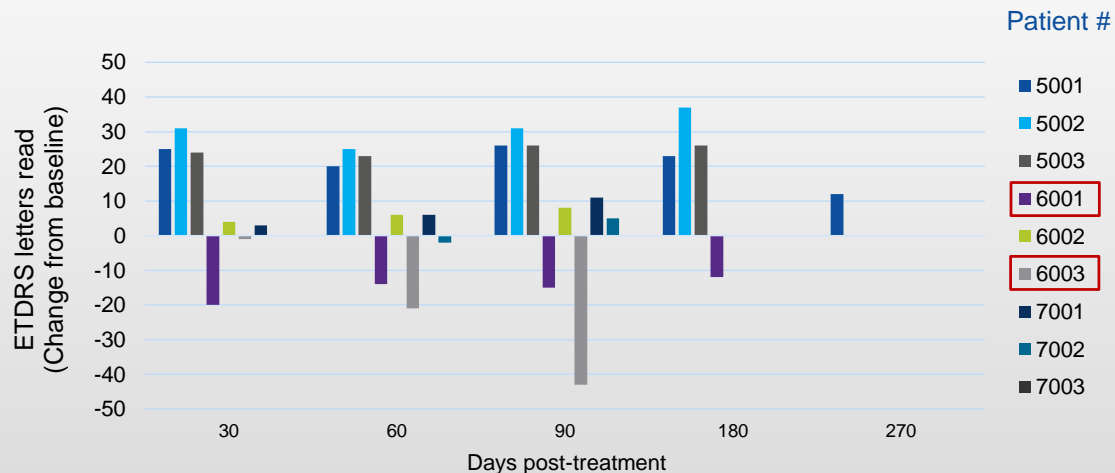
- Massachusetts Eye & Ear Infirmary, Boston, Jason Comander, MD, PhD
- Retinal Research Institute, Phoenix, Pravin Dugel, MD

# Phase 1/2a Summary Results to date\*

- Patient recruitment status:
  - 12 Phase 1 patients treated (>12 months follow up so far)
  - Phase 2a recruitment ongoing:
    - 10 patients treated, follow up period currently:  
1 month: n=8; 3 months: n=6; 6 months: n=4; 9 months: n=1
- Good safety profile (n= 22):
  - No immune-related adverse events
  - No drug product related serious adverse events
  - 2 patients with surgical procedure related vision loss (one AE, one SAE):
    - Consistent with nature of sub-retinal injection procedure; one moderate and likely permanent, the other severe, but improving
- Clinically meaningful efficacy signals consistently seen:
  - Rapid and profound in some patients

# Phase 1/2a Summary Results to date\*

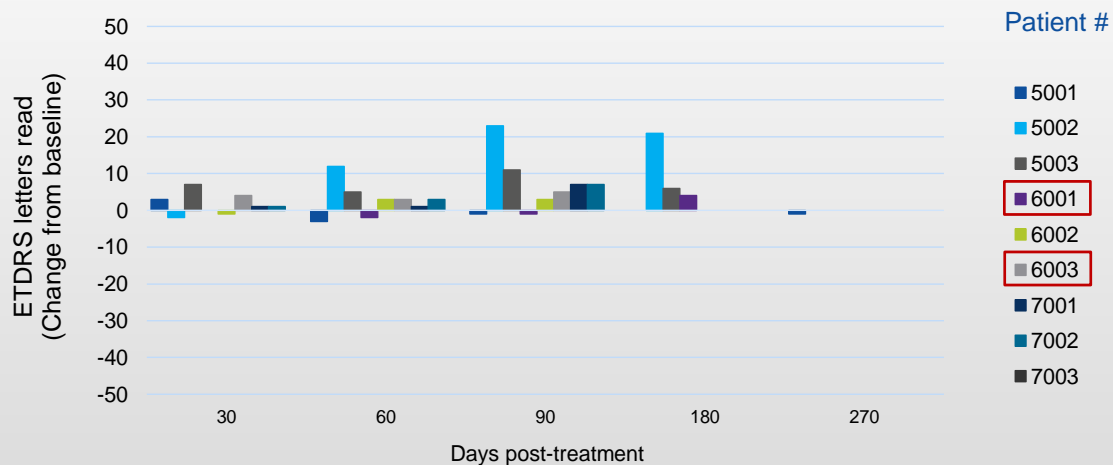
## ETDRS letters read: Phase IIa portion *Change from baseline in treated eye*



# Phase 1/2a Summary Results to date\*

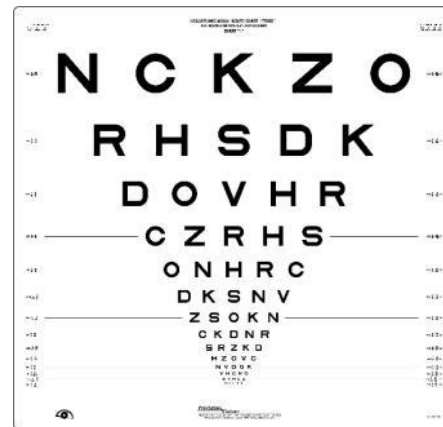
## ETDRS letters read: Phase IIa portion

*Change from baseline in untreated eye*



# Phase 2a Efficacy Results to date\*

Months post-treatment	Mean improvement in visual acuity in treated eye	Mean improvement in visual acuity in treated eye (excluding two patients with procedure-related vision loss)	Mean change in visual acuity in untreated eye
1	+8.3 letters (n=8)	+14.5 letters (n=6)	+ 1.6 letters (n=8)
2	+5.4 letters (n=8)	+13.0 letters (n=6)	+ 2.8 letters (n=8)
3	+6.1 letters (n=8)	+17.8 letters (n=6)	+ 6.8 letters (n=8)
6	+18.5 letters (n=4)	+28.7 letters (n=3)	+ 7.8 letters (n=4)
9	+12.0 letters (n=1)	+12.0 letters (n=1)	- 1.0 letter (n=1)



“We’re excited by the progress of ReNeuron’s hRPC therapy. From the Foundation’s perspective, any gain in vision, or even stabilisation, is a major step forward for patients with RP as currently it is a condition where progressive loss of vision leads to blindness.”

**Benjamin R. Yerxa PhD, Chief Executive Officer — Foundation Fighting Blindness (14 Oct 2019)**

# hRPC Platform Next Steps

- Continue to collect and analyse data from ongoing Phase 1/2 study in RP
  - Further read-outs in H1 2020
- Planning future clinical development programme in consultation with advisors and regulatory authorities
- Assess other indications alongside RP (e.g. Cone Rod Dystrophy)



# CTX Cells



# CTX Cell Therapy



CTX: allogeneic, cryopreserved, human neural stem cell product

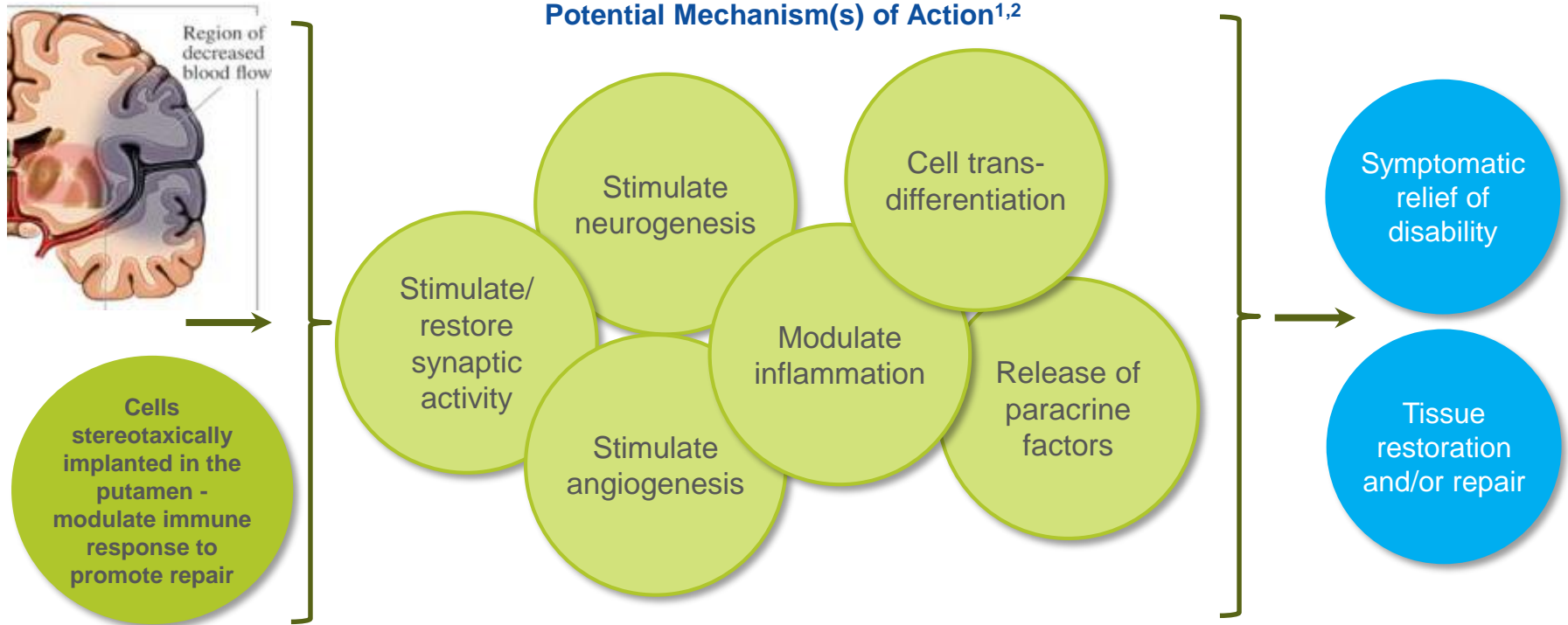
- Promotes anatomical plasticity in the brain
- Excellent safety profile - no immunogenicity issues post-administration
- Manufactured under cGMP with a 12 month shelf life



Commercially Attractive

- Product to be readily ordered, shipped and stored at the hospital
- Delivered in cryo-shipper, controlled thawing at hospital site
- Administer to patient 'on demand'
- Commercial scale manufacturing at attractive COGs

# CTX Promotes Anatomical Plasticity in the Brain



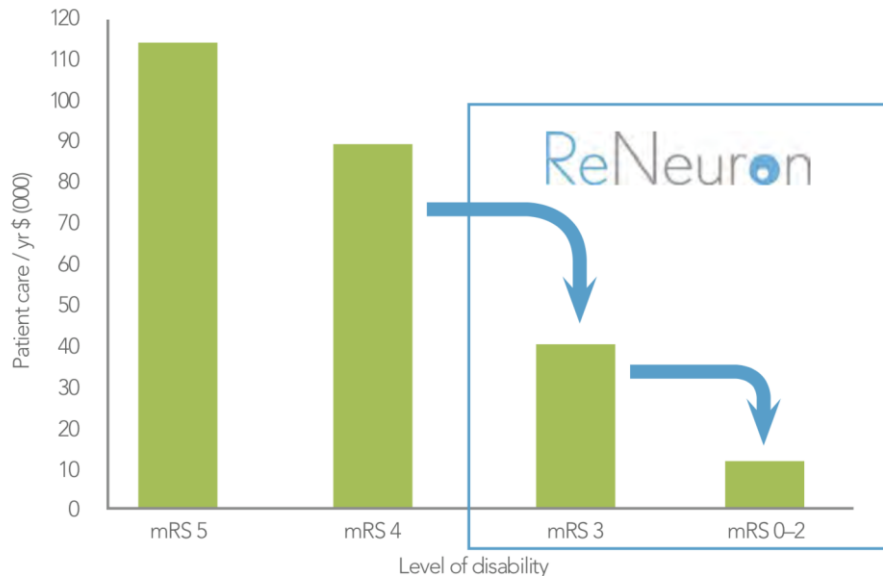
# CTX for Stroke Disability: Unmet Medical Need

- Stroke is the leading cause of morbidity and long-term disability in the U.S.<sup>1</sup>
  - 1 in 6 people will have a stroke in their lifetime
- Financial burden
  - \$34 billion annually in stroke-related costs in the U.S.<sup>1</sup>
  - Direct medical stroke-related costs projected to triple from 2012 to 2030<sup>1</sup>
- Limited treatment options
  - Only one drug available, for use within 4.5 hours of stroke onset<sup>2</sup>
  - Rehabilitation provides most benefit in first month, very little beyond six months<sup>3</sup>



CTX administration promotes repair in the damaged brain

# Severity of Functional Disability Measured by Modified Rankin Scale (mRS)



Source: Company data; adapted from Lekander et al 2017, 42,114 patients from 2007-2012, costs from Sweden translated into \$

mRS 5: Bedridden, requires constant help from others



mRS 4: Needing help to walk, use toilet, bathe



mRS 3: Can walk with appliance, needs some help at home



mRS 0-2: Slight to no disability



**Reductions in disability result in substantial reductions in patient care costs**

# CTX in Stroke Disability: PISCES II Study Results

Phase 2a, single arm, open label study

- 23 disabled, stable stroke patients, 2 to 12 mos post-stroke
- 20 MM CTX cell dose
- Clinically meaningful improvements in disability scales measured out to 12 months post-implantation
- No cell-related safety issues identified

**Very promising results for chronic stroke disability, supportive of a larger, randomised, placebo-controlled Phase 2b study**

Time		Total subjects		Patients with NIHSS upper limb score < 4 at baseline	
Month	N	Responders* (%)		N	Responders* (%)
Baseline	23	-		14	-
3	23	7 (30.4%)		14	6 (42.9%)
6	22	6 (27.3%)		13	5 (38.5%)
12	20	7 (35.0%)		12	6 (50.0%)

\*number of subjects with  $\geq 1$  point improvement in mRS (% of N observed at day of visit)

**Greatest mRS improvements in subjects with residual movement of the affected arm (NIHSS UL <4)**

# PISCES III Study Design and Status



## Phase 2b, Randomised, Placebo-Controlled Study

110 subjects - 1:1 randomization to placebo (sham) surgery

- Age 35-75 inclusive
- Ischemic stroke that includes supratentorial region (CT/MRI confirmed)
- 6-12 mos post-stroke
- mRS 3 and 4
- Some residual arm movement

### Primary Endpoint\*

- >1 pt improvement from baseline in mRS at 6 mos post-treatment

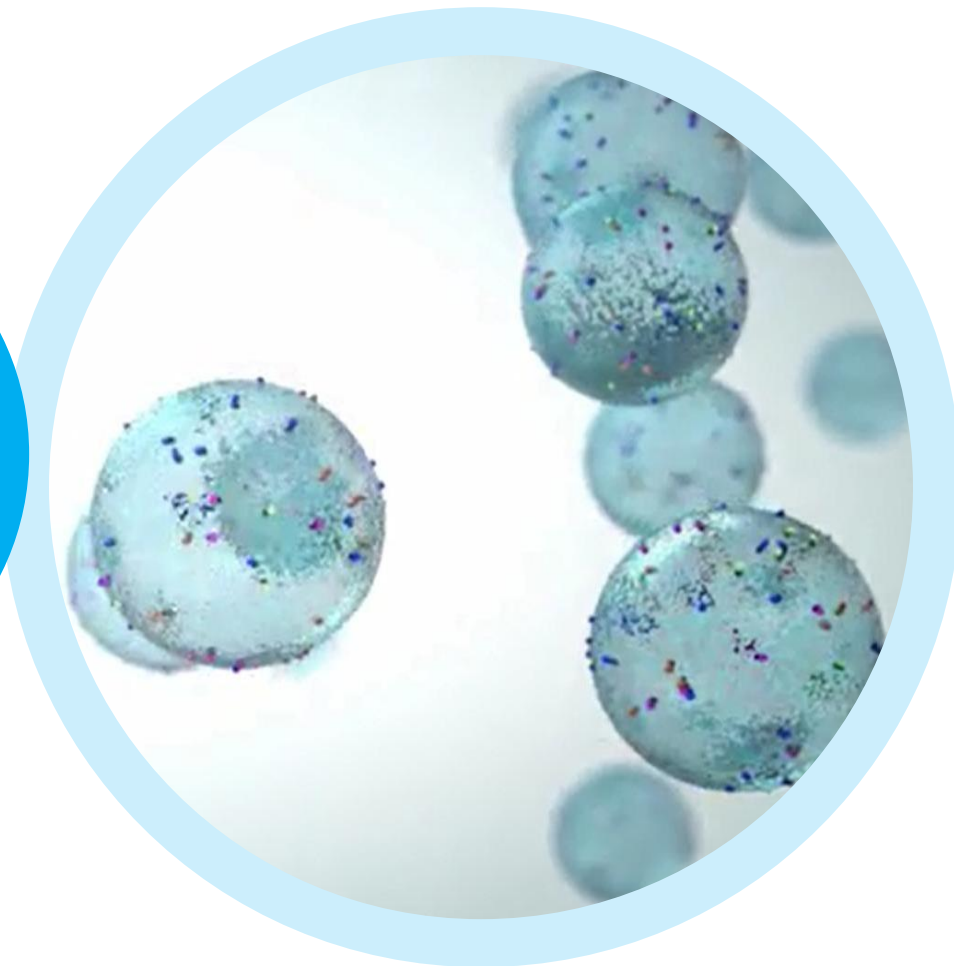
### Secondary Endpoints\* (1, 3, 6, 9, 12 mos post-tx)

- Barthel Index (ADL independence)
- Timed Up and Go test (lower limb and trunk function)
- Chedoke Arm/Hand Activity Inventory (upper limb function)
- NIHSS (impairment scale – neurological outcome and recovery)
- Fugl-Meyer Assessment (performance-based impairment index)
- EQ-5D-5L (QoL)

## Current Status

- 15 surgical sites and 22 patient assessment sites identified and approved
- Initial sites activated and patient dosing in progress
- CTX Drug Product batches in stock or scheduled for manufacture
- Top-line read-out expected in H1 2021

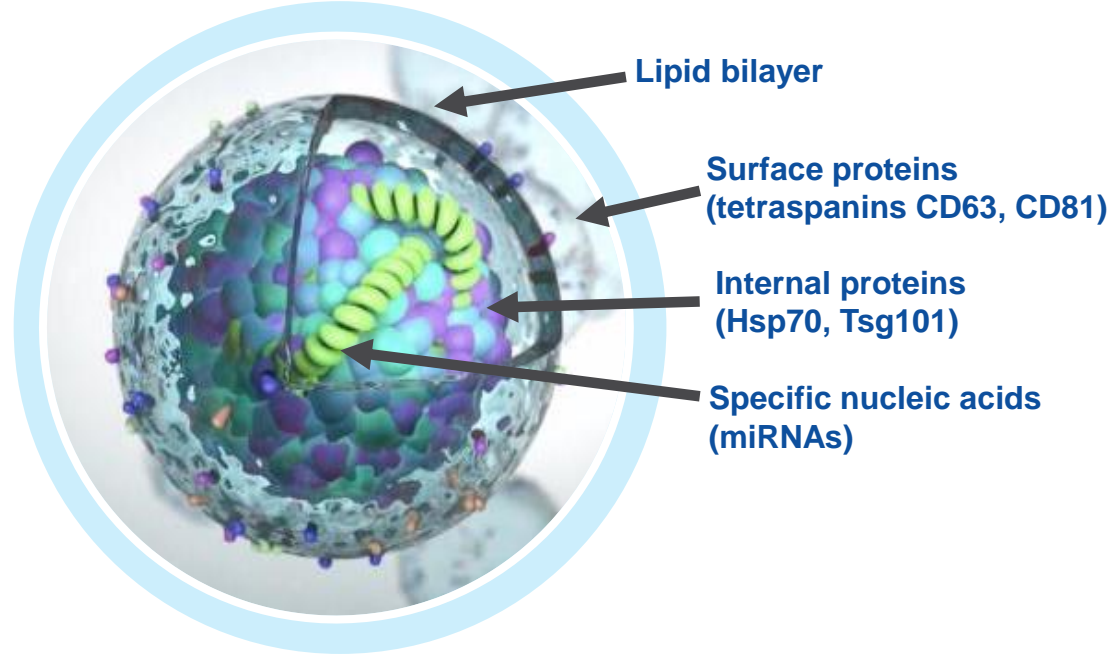
# CTX- Derived Exosomes





# CTX-Derived Exosomes: Biological Nanoparticles

- Nano-scale vesicles released by most cell types as a means of intercellular communication
- Naturally-occurring liposomal delivery system
- Contain and transport bio-active lipids, proteins and nucleic acids



**ExoPr0**

- First CTX-derived exosome candidate
- Potential as a drug delivery vehicle and as a therapeutic

# ReNeuron's CTX-Derived Exosome Technology

## Advantages of exosomes as a delivery vehicle

- Natural carrier of nucleic acids and proteins, amenable for loading complex, hard-to-deliver therapeutic agents
- Ease of bioengineering
- Low immunogenicity
- Intrinsically durable, membrane texture order of magnitude harder than synthetic liposomes

## Advantages of ReNeuron's ExoPr0 exosome technology

- Stable, consistent, high-yield, clinical-grade product
- Fully qualified xeno-free, optimised, scalable GMP process
- Established analytics
- Proven ability to load miRNA and proteins
- Modifiable to carry siRNA/mRNA, CRISPR/Cas9 proteins, small-molecule inhibitors
- Favourable distribution across the blood brain barrier
- Engineered to target particular tissues

# Summary



# Summary

- ❖ A global leader in cell-based therapeutics – sites in UK and Boston, US
- ❖ Allogeneic stem cell technology platforms – patented, scalable & cost effective
- ❖ Targeting diseases with large unmet medical needs
- ❖ Significant clinical milestones in retinal and stroke programmes over the next 24 months
- ❖ Near/medium term opportunities for value-generating partnering/collaboration deals



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